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| 09/308,725 | 01/13/2000 | Ajit Lalvani | GRT/3773-19 | 6572 |

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NIXON & VANDERHYE, PC
901 NORTH GLEBE ROAD, 11TH FLOOR
ARLINGTON, VA 22203

| EXAMINER | |
|---|---|
| CHEN, STACY BROWN | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/308,725 | LALVANI ET AL. | |
| | Examiner | Art Unit | |
| | Stacy B. Chen | 1648 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *13 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *40-58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 May 1999* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/13/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

1. Applicant's amendment filed July 13, 2007 is acknowledged and entered. Claims 40-58 are pending and under examination.

### *Summary of the claimed invention and claims interpretation*

2. The claims are drawn to a method of assay in which peptide-specific effector T-cells are enumerated, which method comprises:

a. providing a fluid containing fresh T cells, which have not been cultured *in vitro*, in contact with a surface carrying an immobilized antibody to interferon-γ (IFN-γ),
b. presenting to the T cells a T cell-activating peptide,
c. incubating the fluid to cause release of said IFN-γ, and
d. detecting release IFN-γ bound to said immobilized antibody to enumerate said peptide-specific effector T cells.

The incubation is continued for a time to permit IFN-γ release by only those T cells that have been pre-sensitized *in vivo* to the T cell-activating peptide and are capable of immediate effector function without the need to effect division/differentiation by in vitro culture in the presence of the T cell-activating peptide; and said method being applied to diagnosis or monitoring of infection with an intracellular pathogen. Specifically, the intracellular pathogen is selected from the group consisting of hepatitis B (HBV), hepatitis C (HCV), *M. tuberculosis*, *P. falciparum*, human immunodeficiency virus (HIV), and influenza virus. New claims 51-58 are directed specifically to the monitoring of *M. tuberculosis*. The T cell activating peptide is of 7-12 amino acid residues in length. The peptide is added to the T cell containing fluid, which is recognized by $CD8^+$ T cells. The peptide is a pre-determined, more specifically, the peptide is the *M. tuberculosis* ESAT-6 peptide. The T cells are peripheral blood mononuclear cells (PBMCs). Particularly, the T cells are taken from a patient known to be suffering, or to have suffered from,

infection with an intracellular pathogen. The fluid mixture is incubated under non-sterile conditions. The incubation is continued for a time of 4 to 24 hours.

The claimed assay in intended to monitor progress of HIV infection. The method is also intended to monitor the effect of a vaccine. The Office maintains its position that the subject matter of claims 49-50 is non-limiting because the claims recite, "The method as claimed in claim 40 performed to monitor progress of HIV infection". There is no active monitoring step given the claim language. The Office interprets claims 49-50 as essentially saying, "The method as claimed in claim 40, used for performing the monitoring of progress of HIV infection". Such a limitation does not carry patentable weight, as there are no active steps in the claims that indicate monitoring the progress or effect of an infection or vaccine.

### *Claim Rejections - 35 USC § 103*

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 40 and 43-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miyahara *et al.* (*Journal of Immunological Methods*, 1995, 181:45-54, "Miyahara") in view of Hagiwara *et al.* (*AIDS Research and Human Retroviruses*, January 20, 1996, 12(2):127-133, "Hagiwara"). Previously, claims 45 and 49-50 were not included in this rejection. The claims are summarized above.

Miyahara discloses the quantification of antigen specific $CD8^+$ T cells specific for the epitope SYVPSAEQI of a rodent malaria antigen using an ELIspot assay. The mice were previously immunized with *Plasmodium yoelii.* Miyahara performed the ELIspot assay with a murine $CD8^+$ T cell clone, YA26, which recognizes a class I MHC restricted epitope (SYVPSAEQI) of the CD protein of *P. yoelii* (page 47, "Results"). After the antigen stimulation, IFN-γ secreted by $CD8^+$ T cells was measured and cells were enumerated. Miyahara does not disclose the use of fresh T cells that have not been cultured *in vitro.*

However, Hagiwara teaches that ELIspot results are divergent when studying PBMCs that have been cultured and stimulated *in vitro.* While Hagiwara's disclosure is directed to cytokine production in HIV patients, the same concept applies to Miyahara's ELIspot. Hagiwara teaches that since the type and amount of cytokine produced *in vitro* can be altered by the culture conditions employed, inconsistent results from such studies are not unexpected (page 131, first column). Hagiwara chose an alternative strategy, which was to study cells actively secreting cytokines *in vivo.* Hagiwara's technique monitored the pattern of cytokines produced by cells participating in ongoing immune responses in HIV-infected individuals (see Hagiwara, page 128). The assay in which peptide-specific effector T-cells are enumerated in Hagiwara's method, comprises the following steps. Phrases in quotations are recitation of the instant claims. The examiner uses the quotations to match the recitations of the claims with the teachings of Hagiwara.

a) providing PBMCs from HIV-infected subjects ("a fluid containing fresh T cells") which have not been cultured *in vitro*, in contact with a 96-well nitrocellulose-backed

micro titer plate coated with anti-cytokine antibodies ("a surface carrying an immobilized antibody to interferon-γ"),

b) stimulating the cells with a 1:100 dilution of phytohemagglutinin ("presenting to the T cells a T cell-activating peptide"),

c) incubating the fluid for 6 hours at 37°C in a humidified 5% $CO_2$ in air incubator ("incubating the fluid to cause release of said IFN-γ"), and

d) overlaying the wells with biotinylated anti-cytokine antibody for 2 hours; then washing the plates; then treating with a 1/300 dilution of avidin-conjugated alkaline phosphatase for 1 hour; then washing a final time, then visualizing the single cells secreting cytokine by adding a solution of BCIP-NBT to the plates, ("detecting release IFN-γ bound to said immobilized antibody to enumerate said peptide-specific effector T cells");

wherein incubation is continued for a time to permit IFN-γ release by only those T cells that have been pre-sensitized *in vivo* to the T cell-activating peptide and are capable of immediate effector function without the need to effect division/differentiation by *in vitro* culture in the presence of the T cell-activating peptide.

It would have been obvious to incorporate Hagiwara's teachings into Miyahara's method. One would have been motivated to use fresh T cells in Miyahara's method in view of Hagiwara's teachings about how the type and amount of cytokine produced *in vitro* can be altered by the culture conditions employed and that inconsistent results from such studies are not unexpected. Given this teaching, one of ordinary skill in the art would have been motivated to reduce inconsistent results by using fresh T cells, rather than the cells used by Miyahara that were

cultured *in vitro* prior to the ELIspot assay. One would have had a reasonable expectation of success that the use of fresh T cells in Miyahara's method would have worked because Hagiwara's method uses fresh T cells in an ELIspot assay.

With regard to claim 45, Miyahara/Hagiwara teach the claimed method/protocol, but both are silent on the embodiment wherein the fluid mixture (T cells and activating peptide) is incubated under non-sterile conditions. The specification does not define exactly what conditions are encompassed by "non-sterile conditions" during incubation. Regardless, it would have been obvious to one of ordinary skill in the art to forego the benefits of sterile conditions during incubation, step (c) of the method. The method does not require that the results be of any particular quality or accuracy as a result of sterile or non-sterile conditions.

With regard to claims 49-50, the Office does not give patentable weight to the intended uses recited. There is no active monitoring step given the claim language. The Office interprets claims 49 and 50 as essentially saying, "The method as claimed in claim 40, used for performing the monitoring of progress of HIV infection", or "used for performing the monitoring the effect of a vaccine", respectively. Such a limitation does not carry patentable weight, as there are no active steps in the claims that indicate monitoring the progress or effect of an infection or vaccine. One may use the method for whatever purpose desired. If Applicant intends for the monitoring of HIV and vaccine to be active steps, the methods must recite the step in either the claim preamble, or as an active step in the protocol.

5. Claims 40-43, 45-48 and 51-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Surcel *et al.* (*Immunology*, 1994, 81:171-176, "Surcel"), in view of Sørensen *et al.*

(*Infection and Immunity*, 1995, 63(5):17170-1717, "Sørensen"), and Hagiwara *et al.* (*AIDS Research and Human Retroviruses*, January 20, 1996, 12(2):127-133, "Hagiwara").

Surcel discloses Th1/Th2 profiles in tuberculosis, based on the proliferation and cytokine response of blood lymphocytes to mycobacterial antigens. "Proliferation and cytokine production profiles by blood mononuclear cells in response to in vitro stimulation with mycobacterial antigens were compared in patients with active tuberculosis and in sensitized healthy people", page 171, abstract. Surcel uses the ELIspot assay to measure effector T cells that produce IFN-γ. Surcel's method uses freshly isolated PBMCs from patients with active tuberculosis. The cells are incubated in 96-well plates for 72 hours, in the presence of antigen, before transfer to anti-IFN-γ antibody-coated nitrocellulose-bottomed plates in the presence of a. mycobacterial antigen. The cells were then incubated for 20 hours and subsequently enumerated (page 172, second column, last three paragraphs). Surcel is silent on the ESAT-6 mycobacterial antigen.

However, Sørensen discloses the discovery of a low-molecular-mass T-cell antigen secreted by *Mycobacterium tuberculosis*. Sørensen teaches that ESAT-6 is a 6-kDa early secretory antigenic target. Sørensen discloses that native and recombinant ESAT-6 elicited a high release of IFN-γ from T cells isolated from memory-immune mice challenged with *M. tuberculosis* (abstract).

It would have been obvious to use ESAT-6 as the activating peptide in Surcel's ELIspot method. One would have been motivated to use ESAT-6 because it is a T cell epitope. Surcel's method is aimed at studying the relationships between epitope specificity and T cell function (page 172, first column, first paragraph). One of ordinary skill in the art would have been

motivated to use Sørensen's antigen as the activating antigen in order to understand the relationship between the ESAT-6 specificity and T cell function. One would have had a reasonable expectation of success based on Sørensen's disclose that ESAT-6 elicited a high release of IFN-γ from T cells isolated from memory-immune mice challenged with *M. tuberculosis*.

Surcel's measurement of IFN-gamma producing T cells involves incubation of T cells in the presence of a T cell-activating peptide for, what is reasonably deduced from the context of the protocol, 72 hours (page 172, second column, fourth full paragraph). The incubation of T cells with T cell activating peptide for 72 hours would allow memory T cells to proliferate, thus the measurement of IFN-gamma producing T cells would include both the memory T cells and effector T cells. This measurement of both memory and effector T cells is not the instantly claimed invention's method of measuring only effector T cells. However, Hagiwara teaches that ELIspot results are divergent when studying PBMC that have been cultured and stimulated *in vitro*. While Hagiwara's disclosure is directed to cytokine production in HIV patients, the same concept applies to Surcel's ELIspot. Hagiwara teaches that since the type and amount of cytokine produced *in vitro* can be altered by the culture conditions employed, inconsistent results from such studies are not unexpected (page 131, first column). Hagiwara chose an alternative strategy, which was to study cells actively secreting cytokines *in vivo*. Hagiwara's technique monitored the pattern of cytokines produced by cells participating in ongoing immune responses in HIV-infected individuals (see Hagiwara, page 128). The method of assay in which peptide-specific effector T-cells are enumerated, comprises:

a) providing PBMCs from HIV-infected subjects ("a fluid containing fresh T cells") which have not been cultured *in vitro*, in contact with a 96-well nitrocellulose-backed microtiter plate coated with anticytokine antibodies ("a surface carrying an immobilized antibody to interferon-γ"),

b) stimulating the cells with a 1:100 dilution of phytohemagglutinin ("presenting to the T cells a T cell-activating peptide"),

c) incubating the fluid for 6 hours at 37°C in a humidified 5% $CO_2$ in air incubator ("incubating the fluid to cause release of said IFN-γ"), and

d) overlaying the wells with biotinylated anticytokine antibody for 2 hours; then washing the plates; then treating with a 1/300 dilution of avidin-conjugated alkaline phosphatase for 1 hour; then washing a final time, then visualizing the single cells secreting cytokine by adding a solution of BCIP-NBT to the plates, ("detecting release IFN-γ bound to said immobilized antibody to enumerate said peptide-specific effector T cells");

wherein incubation is continued for a time to permit IFN-γ release by only those T cells that have been pre-sensitized *in vivo* to the T cell-activating peptide and are capable of immediate effector function without the need to effect division/differentiation by *in vitro* culture in the presence of the T cell-activating peptide.

It would have been obvious to incorporate Hagiwara's teachings into Surcel's method. Surcel's method is intended for measuring effector T cells (active tuberculosis versus sensitized healthy controls, see Surcel's abstract). One would have been motivated to use fresh T cells in Surcel's method in view of Hagiwara's teachings about how the type and amount of cytokine produced *in vitro* can be altered by the culture conditions employed and that inconsistent results

from such studies are not unexpected. Given this teaching, one of ordinary skill in the art would have been motivated to reduce inconsistent results by using fresh T cells, rather than the cells used by Surcel that were cultured *in vitro* prior to the ELIspot assay. One would have had a reasonable expectation of success that the use of fresh T cells in Surcel's method would have worked because Hagiwara's method uses fresh T cells in an ELIspot assay.

With regard to claim 45, Surcel/Hagiwara teach the claimed method/protocol, but both are silent on the embodiment wherein the fluid mixture (T cells and activating peptide) is incubated under non-sterile conditions. The specification does not define exactly what conditions are encompassed by "non-sterile conditions" during incubation. Regardless, it would have been obvious to one of ordinary skill in the art to forego the benefits of sterile conditions during incubation, step (c) of the method. The method does not require that the results be of any particular quality or accuracy as a result of sterile or non-sterile conditions.

Therefore, the invention as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made.

***Response to Arguments***

6. Applicant's arguments have been carefully considered but fail to persuade. Applicant's substantive arguments are primarily directed to the following:

- Applicant argues that Hagiwara's method of stimulating T cells with the PHA antigen would not have been understood to be stimulating *peptide-specific T cells* at the time of the invention. One of ordinary skill in the art at the time of the invention (1993-1996) would have considered any reference to the phrase "peptide-specific" in the

context of the *in vitro* responses of T cells that are pre-sensitized *in vivo* to antigens as excluding phenomena pertaining to aspects of the molecular interaction of PHA on these cells *in vitro*, except when PHA is the cognate antigen. Applicant further argues that the presentation of PHA to the T cells in Hagiwara's method does not involve presentation of PHA via APCs/MHC, as is intended in the instant invention, and is disclosed as critical to the claimed method. Applicant also asserts that at the time of Applicant's invention, there was an overwhelming body of literature recommending long-term in vitro incubations (of the order of several days) for stimulating T cells in vitro with their cognate antigens. Applicant argues that one of *ordinary skill* in the art would likely have adhered to this conventional wisdom.

- In response to Applicant's arguments, the Office recognizes that Applicant intends step b) of claim 40 to mean that the T cell-activating peptide is presented to the T cells via an APC/MHC. Despite Applicant's attempts to persuade that the meaning of the term "presents" in this context at the time of the invention only encompasses MHC presentation, the Office maintains its position that the term "presents" is reasonably interpreted both narrowly (as MHC presentation) and broadly (as a peptide coming into contact with a T cell). Notably, the specification does not limit the definition of "presents" to MHC presentation or peptides.
- With regard to Applicant argument about incubation time, the Office recognizes that there is a body of literature that suggests long incubation times. However, there is also literature that was available to the public that

suggested a shorter incubation time of 6 hours. Regardless of the reason for the 6 hours incubation, or lack of an immunological reason, the Hagiwara reference discloses a 6 hour incubation period of T cells with a T cell activating peptide. That the person of ordinary skill in the art would have adhered to the body of literature that suggests long incubation times and ignored as irrelevant the teaching to incubate for six hours is Applicant's opinion. The 6-hour incubation is a specific teaching by Hagiwara, not a teaching that is merely asserted as obvious by the Office. Since the method was available to the public, it too is reasonably considered to be conventional wisdom.

- Applicant argues that one of ordinary skill in the art at the time of the invention would have known about the induction kinetics of interferon in lymphocytes by PHA *in vitro*, yet, by 1994 (date of the Klinman protocol describing ELISPOT) no had suggested the application of short incubation times to facilitate activation of T cells by their cognate antigens *in vitro*. Applicant asserts that the absence of such an assay in the art strongly supports the view that the mode of action of PHA in vitro was not considered to be germane to the mechanisms of activation of the primary immune response *in vitro*. Applicant also asserts that the senior author of Hagiwara, Dennis Klinman of Klinman *et al.* (1994), suggested long incubation times to stimulate T cells and did not arrive at the claimed invention using Hagiwara's teachings, (teachings which, according to Applicant, disclose nothing new regarding the ELISPOT assay). Applicant asserts that the absence of such teaching in the art, such

as from a recognized expert like Klinman, is an indicator that the Examiner is using improper hindsight.

- Applicant's attempts to use the absence of another arriving at the claimed invention as evidence of non-obviousness are not persuasive. Just because another did not teach the instantly claimed assay or an aspect of that assay does not mean that the concept or assay was not obvious.

- Applicant asserts that Hagiwara's method measures the general level of a non-specific response of a population of cells in PBMCs that are activated by PHA, a mitogen, not the enumeration of antigen-specific effector T cells.
  - In response to Applicant's arguments, note that the claims recite "presenting to the T cells a T cell-activating peptide". Presenting (contacting) PHA peptide to T cells activates the T cells. Step b) of claim 40 does not say that the peptide activates only effector cells because Applicant reasons that the short incubation time of the cells (less than 24 hours) will only give the peptide enough time to activate the effector T cells. Based on Applicant's reasoning, the 6 hour incubation time of PHA with the T cells will only allow the PHA to activate the effector T cells.
- Applicant outlines seven concepts (see Annex I submitted in the response filed July 13, 2007) required to arrive at the claimed invention. Applicant argues that Miyahara teaches, at best, one of the concepts, which is that ELISPOT is a sensitive method that is able to enumerate responsive peptide-specific T cells *in vitro*. Applicant also argues that concept 4, (effector T cells potentially provide a dynamic marker for

intracellular pathogens), was not known prior to Applicant's invention. Applicant further argues that Hagiwara does not use fresh T cells because the word "fresh" does not appear in the text of the reference, nor does Hagiwara appreciate the use of fresh T cells.

- In response to Applicant's arguments, the seven concepts have been considered. Note that the recognition of all seven concepts is not a requirement to arrive at the conclusion of obviousness. One of ordinary skill in the art may have a different reason for combining the teachings and still arrive at the claimed invention. Hagiwara's technique monitored the pattern of cytokines produced by cells participating in ongoing immune responses in HIV-infected individuals (see Hagiwara, page 128). This alternative approach was spurred on by Hagiwara's observation that since the type and amount of cytokine produced *in vitro* can be altered by the culture conditions employed, inconsistent results from such studies are not unexpected (page 131, first column).
- With regard to the word "fresh", the Office acknowledges that Hagiwara does not use the term "fresh". However, Hagiwara's providing PBMCs from HIV-infected subjects ("a fluid containing fresh T cells") which have not been cultured *in vitro* meets the limitation of the claims, and are therefore reasonably considered "fresh". Note that "fresh" is a relative term, and the Office has interpreted the term in the context of the claims, namely, cells that have not been cultured *in vitro*.

- Applicant argues that Hagiwara's disclosure is primarily directed to assays that do not use PHA stimulation. Applicant points to page 131, paragraph 3 of Hagiwara as stating that "divergent results were generally obtained by studying PBMC that had been cultured and stimulated *in vitro*". Applicant notes that these divergent results were obtained using PHA, as references were cited that involve the use of PHA. Applicant argues that this teaching in Hagiwara teaches away from the use of PHA to stimulate cultured cells *in vitro* in order to achieve consistent results. Applicant points to paragraph 5 on page 131 of Hagiwara as evidence that Hagiwara actually suggests the alternative method of measuring cytokine production *in vivo* without addition of stimulating agents *in vitro*. Applicant asserts that this teaching would lead one of ordinary skill not to use PHA if consistent results are desired. Applicant argues that Miyahara teaches precisely what Hagiwara advises against. Applicant asserts that one would have been motivated to use the ESAT-6 antigen in Surcel's method, but that the combination would not have resulted in the instant invention because Surcel's method does not distinguish between effector T cells and memory T cells. Further, there is no motivation to combine Hagiwara's teachings with Surcel's assay because Hagiwara does not use antigens and advises against the use of antigens/mitogens.

  - In response to Applicant's arguments, the teachings of Hagiwara are intended to provide what is lacking from Miyahara's disclosure. Miyahara discloses an ELISPOT assay that meets all of the instant claim limitations with the exception of using cells that have not been culture *in vitro* prior to

peptide activation. The instant obviousness rejection(s) do not assert that it would have been obvious to use the PHA antigen of Hagiwara, rather, it would have been obvious to use cells that were not cultured *in vitro* as opposed to cells that were incubated for days prior to T cell activation. The Office is not attempting to bodily incorporate the teachings of Hagiwara into the teachings of Miyahara.

- Applicant argues that Applicant's invention is a major immunological advance and a commercial success because of unexpected advantages of the assay. Applicant points to their paper, Lalvani *et al.*, in *J. Exp. Med.*, 1997, 186:859-865, of record, which first disclosed these concepts to the public and has been cited numerous times in the immunological literature. Applicant also points to the T-SPOT.*TB* test, encompassed by the pending claims, which is already having a major impact on global disease. Applicant also argues that the instant invention is the subject of a granted patent in Europe, which was maintained as EP 0941478 B2 following opposition proceedings at the EPO. Applicant notes that the Opposition Decision did not mention the Hagiwara reference.
  - In response to Applicant's arguments, the Office has considered the Lalvani paper and is aware that it has been cited in the literature. However, publication and citation of the instant invention is not convincing evidence of nonobviousness.
  - Commercial success abroad, as well as in the United States, is relevant in resolving the issue of nonobviousness. However, the PTO must rely upon

Applicant to provide hard evidence of commercial success. Simply stating that the T-SPOT.*TB* test is having a major impact on global disease is not adequate hard evidence.

- Further, the Office has considered the Opposition decision. However, as Applicant is aware, the Opposition proceedings at the EPO do not influence the PTO's determinations of patentability. Therefore, the invention as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made.

***Conclusion***

7. No claim is allowed.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Stacy B. Chen/ 9-27-2007
Primary Examiner, TC1600